RECOMMENDATIONS FOR THE TREATMENT OF LIPID DISORDERS IN PATIENTS ON PERITONEAL DIALYSIS

ISPD Guidelines/Recommendations

RECOMMENDATIONS FOR THE TREATMENT OF LIPID DISORDERS IN PATIENTS ON PERITONEAL DIALYSIS

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Many patients reach end-stage renal disease (ESRD) with established left ventricular hypertrophy, coronary ischemia, and disseminated atherosclerotic vascular disease. Despite advances in the technology, and analysis of transport kinetics in dialysis, car diovascular morbidity and mortality remain markedly increased in patients on dialysis, and the principal cause of death.

The etiology of vascular disease in the dialysis patient is multifactorial. The focus of this review is on abnormalities of lipid metabolism in these patients, but clearly, attention must be paid to other known and putative cardiac risk factors such as ci garette smoking, hypertension, hypervolemia, and hyperhomocysteinemia.

The past decade has seen the publication of many studies in the nonuremic population, showing statistically significant reductions in cardiovascular mortality with various lipid-lowering therapies. However, because of the lack of long-term controlled stud ies, it remains unclear whether these treatments are applicable to patients with ESRD. On the one hand, because there is such a high prevalence of cardiovascular morbidity and mortality in dialysis patients, one might expect that these therapies would hav e an even more dramatic effect on this “high event” population compared to the general population. On the other hand, the etiology of these abnormalities may be even more complex in the renal failure patient, and it is possible that the treatments given t o the nonuremic population may have surprisingly little benefit in those patients on dialysis.

The purpose of this document is to address the issue of lipid-lowering therapy in patients with ESRD, particularly patients on peritoneal dialysis (PD). The first section will address what is known about the pathogenesis of lipid abnormalities in patients with chronic renal failure. The second section will examine the evidence for abnormalities in lipid metabolism as a risk for vascular disease in patients on PD. The third section will briefly review the lipid-lowering studies that have been performed on the nonuremic population. In the fourth section, we will discuss what is known about the safety and efficacy of the commonly used lipid-lowering drugs in the renal failure population. In the final section, we will give the recommendations, as of 1998, as to what we can hope for using lipid-lowering therapy in our patients on PD.

Lipid Disorders in Peritoneal Dialysis Patients: Description and Pathogenesis

While water-soluble substances such as glucose and amino acids are transported in aqueous solution in the blood, transport of the water-insoluble lipids involves the participation of a range of complex molecules. Lipids may be either “simple” (cholesterol and nonesterified fatty acids) or “complex” (cholesterol esters and glycerol esters). Because of their insolubility in plasma, all lipids are transported associated with “apoproteins,” forming lipoprotein complexes. These complexes contain varying propor tions of triglycerides, phospholipids, and cholesterol and its esters. Partial exceptions are the nonesterified fatty acids, of which 99% are transported bound to albumin.

Apoproteins: Apoproteins have functions other than enabling transport of lipids. Some serve to define the type of receptor with which the lipoprotein can bind, while others serve to activate lipoprotein-specific enzymes, or may themselves be enzymes.

Five groups of apoproteins have been identified (ApoA to ApoE). The ApoA- and ApoB-containing lipoproteins are the two major classes. In some cases, there is more than one gene for each group, in which case they are specified by postscripts such as “ApoA- I” and “ApoC-II.” Furthermore, polymorphisms of these gene loci, which may confer increased susceptibility to certain diseases, exist within the general population. For example, three different alleles (E2, E3, and E4) at the ApoE gene locus code for thre e different protein isoforms, ApoE2, E3, and E4, respectively, resulting in six different phenotypes. Apoproteins for which a definite role has been identified are listed in Table 1.

Lipoproteins: Separation of lipoproteins by density yields five major fractions. These are, in order of decreasing density, high density lipoproteins (HDL), low density lipoproteins (LDL), intermediate density lipoproteins (IDL), very low destiny lipoprot eins (VLDL), and chylomicrons. HDL, LDL, IDL, and VLDL are all derived from endogenous lipid components, whereas chylomicrons are manufactured in the Golgi apparatus of intestinal mucosal cells, from dietary fat. All lipoproteins carry all types of lipid, but in different proportions, so that the density is directly proportional to the protein content and inversely proportional to the lipid content (Table 2).

TABLE 1
Functional Roles of Some Specific Apolipoproteins

Apoprotein	Identified role
ApoA-1	Activates lecithin-cholesterol acyltransferase (LCAT)
ApoB-100	Facilitates binding of LDL particles to LDL receptors
ApoB-48	Facilitates binding of chylomicron remnants to liver receptors
ApoC-II	Activates lipoprotein lipase
ApoD	Transfers cholesterol esters from HDL3
ApoE	Facilitates binding of chylomicron remnants to liver receptors

A subpopulation of LDL has been identified in which an additional protein is attached to ApoB-100. This accessory protein has been called apolipoprotein(a), and the particles carrying it, lipoprotein(a), or Lp(a). This apolipoprotein is very similar in st ructure to plasminogen and may share its ability to bind to fibrin in blood clots, thereby bringing LDL into areas where tissue repair is required, and providing cholesterol for manufacture of new plasma membranes. Whether this is its role or not remains to be seen, but paradoxically its circulating concentration has been shown to strongly positively correlate with the occurrence of atheromatous vascular disease (1).

Lipoproteins and Renal Disease: In recent years, much attention has been focused on the relationship of plasma lipoproteins to vascular disease — the leading cause of death in the Western world. Many studies throughout the world have demonstrated a correl ation between elevated plasma lipid levels (especially cholesterol) and atheromatous vascular morbidity and mortality.

In patients with renal disease, lipoprotein metabolism is altered. This is more closely reflected in the apolipoprotein profile than the lipid profile, and may therefore not always result in hyperlipidemia (2). It follows that simple measurements of plasm a cholesterol and triglyceride concentrations probably underestimate the extent of “uremic dyslipoproteinemia.” Nevertheless, chronic renal failure is usually associated with an increased prevalence of hypertriglyceridemia and lipoprotein abnormalities, i ncluding increased VLDL and LDL, with decreased HDL (3,4).

In general, alterations of lipoprotein concentrations result from an imbalance between lipoprotein synthesis and degradation. In renal disease, lipolytic enzyme activity is known to be reduced — in particular lipoprotein lipase (LPL), hepatic triglyceride lipase (HTGL), and lecithin-cholesterol acyltransferase (LCAT) (2). The underlying mechanisms for reduced LPL activity are unclear, but may include functional insulin deficiency or resistance (possibly mediated by vitamin D deficiency/hyperparathyroidism), and the presence of a nondialyzable inhibitor of LPL in the plasma of uremic patients. The reduced activity is detectable at a glomerular filtration rate of 50 mL/min, which may go some way to explaining the ongoing lipid abnormalities found in many tr ansplant patients.

Reduced LPL activity results in delayed hydrolysis of ApoB-containing lipoproteins and preferential enrichment of partially delipidized, triglyceride-rich particulates with ApoC polypeptides. Individual variations in lipoprotein production rates, LPL and HTGL activities, and the composition of lipoproteins will determine plasma lipid and lipoprotein levels; but in general, the end result is a decrease in levels of nonartherogenic ApoA-containing lipoproteins, and an increase in levels of proatherogenic Ap oC-III enriched ApoB-containing lipoproteins of very low and low density properties. (See Ref. 2 for an in-depth review of these abnormalities.)

TABLE 2
Characteristics of the Five Major Lipoprotein Groups

Density	Diameter	Cholesterol	Triglyceride	
Lipoprotein	(g/mL)	(nm)	(%)	(%)
HDL	1.063–1.210	8	~20	~6
LDL	1.019–1.063	22	55–65	~10
IDL	1.006–1.019	27	~38	~23
VLDL	<1.006	43	15–20	~60
Chylomicron	<0.950	500	~5	~85

HDL = high density lipoproteins; LDL = low density lipoproteins; IDL = intermediate density lipoproteins; VLDL = very low destiny lipoproteins.

Lipoprotein(a) levels are two to three times higher in uremic patients than in controls (5,6). Hyperparathyroidism has been shown to influence lipid metabolism in experimental chronic renal failure, but its importance in the clinical setting is unknown (7).

Lipoproteins and Peritoneal Dialysis: The characteristic lipoprotein abnormalities described in PD patients have recently been thoroughly reviewed by Wheeler (8). Dialysis does not correct uremic dyslipoproteinemia, but may alter its pattern (9). Several studies have shown that, once dialysis commences, continuous ambulatory peritoneal dialysis (CAPD) patients develop a somewhat different and probably more atherogenic lipoprotein profile than do hemodialysis (HD) patients (10–15).

Not all reports agree on the exact differences between the two treatment modalities, but this may not be surprising when one considers that the studies come from ethnically and geographically distinct populations such as northern Europe, southern Europe, and the U.S.A. Furthermore, bias in patient and modality selection will vary from one center to the next. However, compared with uremic patients or those on HD, CAPD patients appear to have higher LDL and total cholesterol concentrations with similar or l ower HDL levels (10–12). Llopart reports a more marked elevation in triglyceride levels in Spanish patients, reflecting a twofold increase in IDL mass and greater triglyceride enrichment of VLDL, IDL, and LDL (15).

In an attempt to overcome the difficulties of cross-sectional studies, Avram et al. prospectively measured serum total cholesterol, HDL, ApoA-1, and ApoB over a 3-year period in 273 CAPD and HD patients (10). Using multiple regression analysis it was foun d that serum albumin, race, gender, and diabetes, but not PTH, independently influenced lipoprotein profiles in both groups of patients. Adjusting for serum albumin and other factors and covariates, triglyceride and HDL levels were similar, but CAPD patie nts had significantly higher total cholesterol, total cholesterol-to-HDL ratios, and ApoB levels. Furthermore, CAPD patients also demonstrated a lower ApoA-1-to-ApoB ratio. Patients with diabetes tended to have a lower HDL level but otherwise had lipid pr ofiles similar to other patients.

Interestingly, in Avram's study hyperlipidemia was associated with improved visceral protein status. However, the associated lipid risk was far outweighed by the increased overall mortality of patients with hypolipidemia, suggesting that malnutrition is o f greater prognostic importance than is uremic dyslipidemia. There was a small but significant decline in ApoB levels in this study (16). Other studies have demonstrated no change in lipid and lipoprotein levels over time (11,17). Other shorter longitudin al studies, involving fewer patients, have reported a worsening of lipoprotein abnormalities with time on CAPD (18,19).

A number of factors may be important in producing a different lipoprotein profile in CAPD patients compared to HD patients. Glucose absorption from the peritoneal cavity of CAPD patients varies between 100 – 200 g/day, and results in increased insulin lev els which are thought to enhance synthesis of triglyceride in the liver (11). In addition, protein loss into the dialysate occurs at a rate of 5 – 15 g/day, along with lipoproteins of all type groups. Sieving results in preferential loss of the smaller mo lecules such as HDL, which is lost at a rate equivalent to 34% of its daily synthetic rate (19). This state has been compared to the nephrotic syndrome, wherein hypoalbuminemia is thought to stimulate hepatic lipoprotein synthesis, although a significant difference is that the kidney is not contributing to albumin catabolism in CAPD patients. It has been suggested that peritoneal protein losses upregulate hepatic VLDL production, but the majority of studies have not demonstrated a correlation between trig lyceride or VLDL levels and protein losses or albumin levels in CAPD patients (8,19).

Several studies have specifically concentrated on levels of Lp(a) (6,14,20,21) because of its known strong association with atheromatous disease in the general population. All the studies found Lp(a) levels to be two to three times higher in CAPD patients than in healthy controls. Siamopoulos et al. (14) compared Lp(a) levels in CAPD and HD patients and found the levels to be slightly higher in CAPD patients, but the difference was not significant (0.28 vs 0.20 g/L, p = 0.056). In the study of Shoji et al ., median Lp(a) levels were almost twice as high in CAPD patients compared to those on HD. Furthermore, there was an association between Lp(a) levels and a positive history of ischemic heart disease (20). This finding was not confirmed by Anwar et al. (6) , who noted that levels as high as those found in his series occur in fewer than 5% of the general population. The mechanisms that lead to elevated Lp(a) concentrations in CAPD are unclear, and it is not known whether the increase is a result of impaired renal function or of CAPD itself. One possibility is that increased loss of lipoproteins and other plasma proteins into the dialysate may stimulate Lp(a) synthesis in the liver (6,20).

In summary, it would appear that CAPD is associated with a more atherogenic lipoprotein profile than is HD; a summary of the likely abnormalities to be found in well-nourished CAPD patients is shown in Table 3. Factors contributing to this difference may include glucose uptake from dialysis fluid, protein and lipoprotein loss into the dialysis fluid stimulating hepatic VLDL synthesis, and preferential sieving of smaller "protective" HDL molecules. However, detailed mechanisms remain to be elucidated, and it would appear that geographically distinct CAPD populations may exhibit subtly different abnormalities. This is not surprising because genetic and environmental factors will vary.

TABLE 3
Typical Lipoprotein Profile of CAPD Patients Compared to Approximate Means of a Healthy Population

Lipoprotein	Healthful Mean	Effect of CRF/CAPD
Total triglycerides	1.25 (mmol/L)	Increased ×2–×3
Total cholesterol	5.90 (mmol/L)	Increased by 1–2 mmol/L
VLDL cholesterol	0.45 (mmol/L)	Increased ×2–×3
LDL cholesterol	4.00 (mmol/L)	Increased by 0.5 mmol/L
HDL cholesterol	1.30 (mmol/L)	Decreased by 0.2–0.4 mmol/L
Lipoprotein(a)	10.0 mg/dL	Increased ×2–×4
Apolipoprotein B	80 mg/dL	Increased by 50%–100%
Apolipoprotein A1	100–200 mg/dL	Reduced by 10%–50%

CAPD = continuous ambulatory peritoneal dialysis; CRF = chronic renal failure; VLDL = very low destiny lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein.

In view of the findings of Avram et al., a “normal” lipoprotein profile may reflect malnutrition and increased risk of death (16). Any CAPD patient who is found to have a “favorable” lipoprotein profile, as distinct from that shown in Table 3, should be c arefully assessed for signs of malnutrition.

Lipids as a Risk Factor for Vascular Disease in Patients on Peritoneal Dialysis

In subjects without renal disease, elevated cholesterol is a risk factor for ischemic heart disease, and lipid-lowering treatment lowers this risk. This association has not been demonstrated in subjects with ESRD. Cardiovascular disease is the most common cause of death in PD patients. Many patients starting dialysis have pre-existing cardiovascular disease, which is associated with a lower survival on dialysis (22–25). The CANUSA trial and the Italian Cooperative Peritoneal Dialysis Study Group both foun d that cardiovascular mortality relates to disease present at the start of dialysis, and not to some factor associated with dialysis (23,24). However, Khanna et al. found an incidence of de novo ischemic heart disease of 8.8% at 1 year and 15% at 2 years (22), which is higher than that seen in the Framingham cohort.

The studies of whether cholesterol is a risk factor for ischemic heart disease are mixed. Some investigators have stressed risk factors other than lipids, such as left ventricular hypertrophy, hypertension, and abnormal calcium metabolism, to account for the high cardiovascular mortality (26,27). In HD patients, the risk associated with cholesterol is a J-curve (28,29). Lowrie et al. found that the greatest risk was associated with a low cholesterol (<150 mg/dL). The risk then progressively decreased for higher levels of cholesterol until the cholesterol was over 300 mg/dL, at which level the risk increased (29). This study did not see any pattern of risk associated with cholesterol in PD patients. A low cholesterol with a low albumin has been associated with higher mortality in PD patients in some studies (16,30).

This demonstrates the importance of poor nutrition as a risk factor for mortality. The strength of the risk associated with low cholesterol (and malnutrition) may obscure the risk of vascular disease associated with higher levels of cholesterol (16).

Other investigators have seen an association between elevated lipoprotein levels and ischemic heart disease (31–33). Gamba et al., in a retrospective study, found a higher mortality with a low albumin and a low creatinine (indicating poor nutrition), but also with a high cholesterol level (33). Pollock et al. found that patients who survived had a higher average albumin and a lower average triglyceride level (2.95 mmol/L vs 3.84 mmol/L), although this study examined each variable individually and did not use multivariate analysis to control for other covariates (31). Gault et al. found that elevated ApoB levels and an elevated cholesterol/HDL ratio correlated with the severity of ischemic heart disease. An elevated triglyceride level was also associated w ith an increased risk, but the relationship was less strong (32). Furthermore, this study did not examine patients from the start of dialysis, but from the start of the study period. The exclusion of patients who died prior to the start of the study may h ave influenced the results.

Treatment of Lipids in Normal Subjects

In subjects without renal failure, high LDL cholesterol and low HDL cholesterol are risk factors for cardiovascular mortality (34,35). Whether an increased triglyceride level is an independent risk factor for cardiovascular disease (CVD), once adjusted fo r other covariates, is controversial. The triglyceride level is generally inversely related to the HDL level. The Framingham study found that the triglyceride level was a predictor alone (especially in women), but once other factors were taken into accoun t, it was no longer a significant independent predictor of CVD (35). A recent meta-analysis found that the triglyceride level is an independent risk factor, even when adjusted for HDL (36). However, in this meta-analysis, not all of the studies used had c omplete data on other covariates.

Lipid lowering by multiple interventions has been shown to decrease the incidence of cardiovascular events, for both primary prevention trials (37–41) and secondary prevention trials (42–44). The Lipid Research Clinics trial randomized asymptomatic subjec ts to cholestyramine or placebo. The LDL was lowered by 20%, which led to a 19% decrease in nonfatal myocardial infarction (MI), a 24% decrease in CVD death, and a 21% decrease in the need for bypass surgery (38). A significant decrease in overall mortali ty was not seen (observed 7% lower overall mortality) because of an increase in

violent and accidental death.

A similar finding of a lower incidence of MI and CVD mortality with an increase in non-CVD mortality has been seen with fibric acid resins (37). Whether this is a function of chance or related to an effect of the treatment is unclear. More recent trials u sing HMG-CoA reductase inhibitors have produced greater decreases in LDL cholesterol, and have shown a lower incidence of cardiovascular events and a lower overall mortality (40,41,44). In the Pravastatin Multinational Study, subjects assigned to pravasta tin had a 26% lower LDL, which led to a 31% decrease in nonfatal MI, a 28% decrease in CVD death, a 32% decrease in overall mortality, and a 37% decrease in the need for revascularization (40). The 4S trial was a large secondary prevention trial using sim vastatin in subjects with a history of coronary artery disease (44). In the subjects on simvastatin, the LDL was reduced by 35% and there was a 42% lower incidence of CVD death, a 32% lower incidence of nonfatal cardiovascular events, and a 37% decrease i n the need for revascularization. There was no difference in noncardiovascular deaths (44).

A common lipid abnormality in PD patients is hypertriglyceridemia with low HDL levels (see second section). Evidence that treating these abnormalities in the absence of abnormalities in LDL cholesterol is beneficial, is not clear-cut. One trial of clofibr ate and nicotinic acid studied subjects with a history of MI, but did not select subjects based on the type of hyperlipidemia (43). In this trial, hypertriglyceridemia was the most common lipid abnormality seen. Treatment was associated with a 36% lower C VD mortality and a 26% lower incidence in overall mortality. The mortality benefit was seen only in subjects with triglyceride levels above 1.5 mmol/L, and the benefit appeared to be related to the degree of triglyceride lowering. However, this study did not control for changes in HDL cholesterol and was a nonblinded, although randomized, trial.

In the Helsinki Heart Study, there was no consistent relationship between the change in serum triglycerides and the lower incidence of cardiovascular events seen, although the effect was greatest in subjects with elevated baseline triglyceride levels (45) . It should be noted however, that in patients with elevated triglycerides, lowering of LDL cholesterol can have a beneficial impact, even in the presence of other metabolically unfavorable factors such as low HDL cholesterol or raised triglycerides. The Post CABG trial revealed that aggressively reducing LDL cholesterol attenuates the risk associated with unfavorable HDL cholesterol and triglyceride profiles (46).

Treatment of Hyperlipidemia in Peritoneal Dialysis Patients

While a lipid-lowering diet can be moderately effective in HD patients (47,48), no data are available concerning dietary manipulation of plasma lipids in patients on PD (49). At this juncture however, it is important to note that effecting good glycemic c ontrol in diabetic patients on PD may be important in improving lipid abnormalities, particularly hypertriglyceridemia.

There are several studies that examine the effect of pharmacologic therapy on lipid abnormalities in patients on PD. It is clear that the HMG-CoA reductase inhibitors reduce both total and LDL cholesterol in these patients. A recent retrospective analysis of lipid-lowering therapy in patients with different types of renal disease surveyed 18 interventional studies in patients on CAPD. The analysis demonstrated that the HMG-CoA reductase inhibitors reduced total and LDL cholesterol levels, and significantl y increased HDL levels. Furthermore, the fibric acid analogs led to a significant reduction in plasma triglycerides (49). However, as was noted previously in this paper, the treatment benefits from reducing plasma triglycerides alone with regard to cardio vascular disease remain uncertain. The extent of normalization of serum lipids was similar among the different renal disease groups examined, including CAPD patients, those on HD, patients with chronic renal insufficiency, patients with a functioning rena l transplant, and patients with nephrotic syndrome. If anything, patients on CAPD or with nephrotic syndrome had a greater reduction in triglycerides and an increase in HDL cholesterol with HMG-CoA reductase inhibitors, compared to those in the other rena l disease categories. The similarity of response in CAPD and nephrotic patients may be the result of a similarity of pathogenesis of lipid abnormalities in these two groups, that is, loss of protein into the dialysis effluent (PD) or the urine (nephrotic syndrome) (49).

The fibric acids should be dose-reduced to avoid myopathy. Low doses of these agents however do not appear to lead to rhabdomyolysis (49). In the retrospective analysis described, in 18 studies of fibric acid analogs, there were no documented episodes of rhabdomyolysis in 282 patients with decreased renal function, treated for a total of 109 patient-years (49). Although experience with these agents in PD patients is recent, it appears that the HMG-CoA reductase inhibitors do not have to be dose reduced fo r renal failure. However, even in the absence of overt clinical side effects, creatinine phosphokinase (CPK) levels may increase. In one study of CAPD patients, just 10 mg of simvastatin led to as much as a tenfold increase in CPK levels (50). Similar sid e effects have been reported with other agents such as pravastatin (51).

Fish oil supplementation lowers triglycerides in PD patients by approximately 30% (52–55). The effect on other lipoprotein fractions has been variable. Some studies have shown a decrease (54), an increase (52), or no change (53) in HDL. Most studies showe d no change in LDL (52,53,55), although one study did show an increase in LDL cholesterol with fish oil supplementation (54).

Carnitine has been advocated to improve lipids in renal failure patients. Carnitine is involved in mitochondrial transport of fatty acids (56). In patients on HD, plasma and muscle carnitine levels decrease (57). This may lead to neuromuscular symptoms an d increased triglycerides, although this theory is controversial. The effects of supplementation on triglyceride levels in HD patients have been mixed. Some studies have shown an improved lipoprotein profile (lower triglycerides and high HDL) (58–60), whi le other studies have shown no change (61,62) or worsened triglyceride levels (63–65). In PD patients, total plasma or muscle carnitine levels do not appear to decrease with time (57). There are fewer studies of carnitine supplementation done in PD patien ts. Warady et al. did not see an effect on lipids with carnitine supplementation in pediatric PD patients (66). Wanner et al. found that carnitine supplementation led to an increase in triglyceride levels (65).

Recommendations for the Treatment of Lipid Disorders in Patients on Peritoneal Dialysis

As can be noted from the foregoing sections, the following principles are established:

1. Lipoprotein abnormalities are prevalent in patients on peritoneal dialysis.
2. Cardiovascular disease is the most important single cause of death in patients on peritoneal dialysis.
3. Treatment of lipoprotein abnormalities, particularly LDL cholesterol, is associated with reduction in cardiovascular morbidity and mortality in the nondialysis population.
4. Both HMG-CoA reductase inhibitors and fibric acid derivatives effect significant reduction in elevated lipid levels in peritoneal dialysis patients.
5. There is no evidence that improvement in lipid levels leads to a reduction in cardiovascular events in patients on peritoneal dialysis.

Broadly categorized, treatment strategies for hyperlipidemia can be either primary or secondary treatment programs. In primary prevention, a patient is treated because he has a measured abnormality in his lipoprotein profile, but no known coexisting cardi ovascular disease. The WOSCOP Study is an example of a primary prevention intervention (41). Secondary prevention treatment strategies treat patients with a laboratory abnormality in lipoprotein profile only if the individual is known to have pre-existing CVD. Secondary prevention studies include the 4S and CARE trials (44,67).

In patients with renal failure, one must consider whether the incidence of CVD is so high that the coexistence of uremia defines all of our renal failure patients as being at sufficient risk for vascular disease that treatment should be considered within the context of secondary prevention. Such a strategy presupposes that all patients with uremia will have some significant CVD, albeit in many cases asymptomatic. Treatment recommendations are different, depending on whether one chooses to approach patient s with a primary or a secondary prevention strategy. In uremia, this remains an unsettled question and the individual nephrologist must come to some decision in this regard in approaching therapies for patients in a rational fashion.

There is no study that adequately addresses whether or not treatment of lipid abnormalities will alter the course of CVD in uremic patients.

Until such evidence is clearly available, the following treatment strategies are proposed based on current (as of 1998) recommendations from the National Cholesterol Expert Panel, which has recently reduced target levels for LDL cholesterol to levels lowe r than ever before (68) (see Table 4).

Secondary Prevention (Patients with known pre-existing coronary artery disease and perhaps all patients with uremia): LDL cholesterol is to be reduced to less than 2.56 mmol/L (100 mg/dL). HMG-CoA reductase inhibitors should be used as the first-line ther apy to reach these objectives. Liver function and CPK levels should be monitored as part of the routine blood work for the first year. This recommendation is not evidence based, but based on the extrapolation of data from a nonuremic population. In other words, it is assumed that the risk reduction with this class of drugs is at least as great in the dialysis population as it is in the nondialysis population. Should HMG-CoA reductase inhibitors not be tolerated by the patient, the use of bile acid sequest rants can be tried. It should be noted that these drugs are also often poorly tolerated, and may impair gastrointestinal absorption of other medications.

TABLE 4
National Cholesterol Expert Panel Guidelines for LDL-Cholesterol levels

Primary prevention	< 3.33 mmol/L (130 mg/dL)
Secondary prevention	< 2.56 mmol/L (100 mg/dL)

Primary Prevention 1 (No known coexisting atherosclerotic coronary artery disease and discounting uremia as a condition implicating coexistent coronary artery disease): In patients with known additional risk factors for atherosclerosis, and a fasting seru m LDL cholesterol of greater than 4.5 mmol/L, if dietary restriction is ineffective, the target level for LDL cholesterol is less than 3.3 mmol/L. As in secondary prevention treatment groups, HMG-CoA reductase inhibitors remain the first line of therapy t o achieve these targets.

Primary Prevention 2 (In uremic patients with no known coronary artery disease; no additional risk factor, including the absence of a positive family history for coronary artery disease; and a fasting LDL cholesterol between 2.3 and 4.5 mmol/L): In this g roup, if one considers uremia itself to confer sufficient risk to consider all patients to be approached as a secondary prevention group, then target LDL cholesterol would be less than 2.56 mmol/L. If one considers uremia not to be a sufficient risk facto r to assume that all patients have coronary artery disease, then no treatment would be indicated and regular surveillance for significant changes in their clinical status and/or their lipid profile should be monitored on a 6-monthly basis. Should the pati ents then fall into categories “secondary” or “primary 1,” the treatment would be initiated accordingly.

None of these drugs are recommended for use during pregnancy, and caution should be taken for fertile women. Breast feeding is not recommended while using lipid-lowering drugs. Contraindications for use of the statins and the fibrates are known side effec ts to the drug, active liver disease, or increased liver enzymes of unknown origin. Overall caution should be taken in abusers of alcohol and drugs due to the risk for uncontrolled interactions. Patients with hepatitis C should be closely monitored while on these medications. In patients with severe renal impairment there is also a contraindication for the use of clofibrate, niceritrol, and nicotinic acid stated by the manufacturers.

Additional caution is given for patients with inflammatory bowel disease when considering cholestyramine and colestipol. Patients with diabetes mellitus may have an impairment of their glucose metabolism by nicotinic acid drugs, clofibrate, and bezafibrat e.

Erythropoietin has been reported to reduce serum lipids, but this should be considered a bonus, and not an indication for use of this expensive medication (69).

There are no published studies on the role of dietary modification in PD patients and its effect on lipid levels. In principle, however, diet should avoid high levels of cholesterol and saturated fat. This should not be at the expense of protein or energy intake, because protein calorie malnutrition is a serious complication and portends a poor prognosis.

Insofar as the evidence linking elevated serum triglyceride concentration to atherogenic risk is tenuous in the nonuremic population, it is difficult to know what approach should be taken with the hypertriglyceridemic patient. It should be noted however, in patients in whom the serum triglyceride exceeds 2.6 mmol/L, the total serum cholesterol and LDL cholesterol will be inaccurate and potentially misleading, with respect to the nature of the lipid abnormality. In such cases, a measurement of ApoB gives a better index as to whether or not there is truly an elevation in the number of LDL particles, and thus whether treatment is indicated on the basis of an LDL abnormality. For the patient with mildly elevated serum triglycerides, dietary intervention may b e helpful, as mentioned above (70). Attention should be paid to glycemic control in diabetics, and hypertonic dialysate should be avoided, if possible. For more serious hypertriglyceridemia, fibric acid analogs are helpful, since they diminish production of VLDL and stimulate lipoprotein lipase (71).

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